Loss of Bronchoprotection With Salmeterol

To the Editor:

I read with considerable interest the report by Bhagat et al (CHEST 1995; 106:1235-39) in which they describe a “Rapid Onset of Tolerance to the Bronchoprotective Effect of Salmeterol.” They suggest that their findings reinforce the notion that β₂-agonists as regular therapy should be used with caution.

Airway hyperresponsiveness appears to be an important characteristic of asthma, and it may be related to the severity of asthma symptoms. The finding of a reduction in bronchoprotective effect against methacholine with salmeterol use (CHEST 1995; 106:1235-39) is not easily explained. Furthermore, the clinical significance of these findings in terms of patient management has not been clarified to date. Like the study of Bhagat et al, many of the reports 1,3 describing a reduction in bronchoprotection with regular β₂-agonist use included mild asthmatics who were not using regular antiinflammatory medication (either steroid or nonsteroid). At the present time, salmeterol is not recommended for use in patients who are not receiving optional antiinflammatory therapy. Booth et al studied mild-to-moderate asthmatics receiving maintenance inhaled corticosteroids and found that salmeterol provided significant protection against methacholine-induced bronchoconstriction with no significant attenuation of bronchoprotection with 8 weeks of regular use. Furthermore, there are data 5 that suggest that salmeterol use is not associated with any “proinflammatory” effect as reflected by changes in inflammatory cell numbers or activation in bronchoalveolar lavage fluid of asthmatics receiving maintenance-inhaled corticosteroids.

Recently, I have become increasingly concerned about the many patients who present to the clinic indicating that they are reluctant to use their short-acting β₂-agonists (even infrequently) because of the media reports about possible harmful effects with regular use. Given the controversy that exists regarding the potential adverse effects associated with regular use of short-acting β₂-agonists, it is important that we continue to keep patients informed about appropriate treatment strategies, including the use of long-acting β₂-agonists in conjunction with appropriate antiinflammatory therapy. Future studies reporting on the adverse effects of β₂-agonists should also stress the relevance of such findings within the context of current management guidelines.

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REFERENCES

To the Editor:

We thank Dr. D’Urzo for his interest in our article (CHEST 1995; 106:1235-39). We disagree with the concept that what happens in mild, well-controlled asthmatics would not be expected to occur in moderate or severe asthmatics. High-dose inhaled corticosteroid did not prevent the development of tolerance to the bronchoprotective effect of salbutamol vs methacholine nor did it prevent salbutamol-increased airway responsiveness to allergen. To specifically answer Dr. D’Urzo’s query regarding salmeterol, we have demonstrated identical findings in a group of eight asthmatics who required moderate to high doses of inhaled corticosteroids.

To our knowledge, the only investigation that has failed to show tolerance to the bronchoprotective effect of inhaled β₂-agonists is the article noted by Dr. D’Urzo by Booth et al (Thorax 1993; 48:1121-24) in which tolerance did not occur to the small bronchoprotective effect of salmeterol vs methacholine measured 12 h after the last dose. This may be the result of the study design since their subjects were allowed ad-lib use of “rescue” salbutamol at an unspecified rate. We have demonstrated 2 that tolerance to the bronchoprotective effect of inhaled β₂-agonists occurs at the low pg/dl; dose of salbutamol 200 pg/dl; therefore, failure to demonstrate tolerance in the study by Booth et al may, in fact, be because it was already present at the beginning of the study.

β₂-agonist-induced tolerance to the bronchoprotective effect is not confined to mild asthmatics and is not inhibited by inhaled corticosteroids. We remain firm in our belief that the regular use of inhaled β₂-agonists in asthmatics should be avoided if at all possible.

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